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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,763	05/12/2005	Heinz Peter Vollmers	043043-0358749	8912

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EXAMINER	
HALVORSON, MARK	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,763	VOLLMERS ET AL.	
	Examiner	Art Unit	
	Mark Halvorson	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *79-103* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *102* is/are allowed.

6)☒ Claim(s) *79-101 and 103* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 79-103 are pending and under examination.

NEW REJECTIONS:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 79- 99 and 103 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the antibody CM-1 is required to practice the invention. As such, the antibody or hybridoma producing the antibody must be readily available or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If it is not so obtainable or available, the requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the antibody or hybridoma producing the antibody. In the instant case, the hybridoma has been deposited under the terms of the Budapest Treaty but a statement has not been received indicating that all restrictions upon availability to the public will be irrevocably removed upon the granting of the patent, the deposit will be maintained in a public depository for a period of 30 years, or 5 years after the last request for the enforceable life of the patent, whichever is longer, and that the deposit will be replaced if it should ever become inviable

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants, or a statement by an attorney of record over his or her

signature and registration number, stating that the instant invention will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If a deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809 and MPEP 2402-2411.05, Applicant may provide assurance of compliance by affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number showing that:

a) during the pendency of the application, access to the invention will be afforded to the Commissioner upon request;

b) all restrictions upon availability to the public will be irrevocably removed upon the granting of the patent;

c) the deposit will be maintained in a public depository for a period of 30 years, or 5 years after the last request for the enforceable life of the patent, whichever is longer;

d) a test of the viability of the biological material at the time of deposit (see 37 CFR 1.807); and

e) the deposit will be replaced if it should ever become inviable.

Claims 80-94 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 80-94 are drawn to a genus of purified antibodies comprising a heavy chain variable region sequence having from 90, 95 or 98% sequence identity to SEQ ID NO:1, or has an insertion or deletion of one amino acid residue of SEQ ID NO:1, and a light chain variable region sequence having greater than 90, 95 or 98% sequence identity to SEQ ID NO:3, or has an insertion or deletion of one amino acid residue of SEQ ID NO:3, that specifically binds to an epitope of an antigen expressed by at least one of HT-29, CACO-2, COLO-320 or COLO-678 cells, wherein CM-1 antibody specifically binds to said epitope of the antigen expressed by at least one of HT-29, CACO-2, COLO-320 or COLO-678 cells.

The specification discloses an IgM antibody, CM-1, that induces apoptosis of a neoplastic cell but does not induce apoptosis of a non-neoplastic cell wherein the antibody specifically binds to at least one of HT-29, CACO-2, COLO-320, COLO-206F, or COLO-678 cells, the antibody comprising a heavy chain variable region consisting of the amino acid sequence of SEQ ID NO: 1, and a light chain variable region consisting of SEQ ID NO:3. Thus, neither the epitope nor even the specific antigen bound by the claimed antibody is disclosed.

The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

The Federal Circuit has recently clarified that a molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

Thus, the instant specification may provide an adequate written description of the genus of antibodies, per Lilly by structurally describing a representative number of antibodies that function as claimed or by describing structural features common to the members of the genus, which features constitute a substantial portion of the genus. Alternatively, per Enzo, the specification can show that the claimed invention is

complete by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

In this case, the specification does not describe the genus of antibodies in a manner that satisfies either the Lilly or Enzo standards. There are insufficient structural features common to all members of the genus of antibodies. The genus of antibodies encompasses any antibody having one amino acid insertion or deletion at any position of SEQ ID NO:1 or SEQ ID NO:3. The genus also includes antibodies comprising at least 10% amino acid differences from SEQ ID NO:1 or SEQ ID NO:3.

The state of the prior art is such that it is well established in the art that the formation of an intact antigen-binding site of antibodies routinely requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, 3rd Edition, 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA, 79(6):1979-1983, March 1982, previously cited). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Coleman P. M. (Research in Immunology, 145:33-36, 1994) teaches that even a very conservative substitution may

abolish binding or may have very little effect on the binding affinity (see pg. 35, top of left column and pg. 33, right column). While there are some publications, which acknowledge that CDR3 is important, the conformations of other CDRs as well as framework residues influence binding. MacCallum et al (J. Mol. Biol., 262, 732-745, 1996) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col.) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.). Thus, the art discloses that a change of even one amino acid of an antibody may change the ability of that antibody to bind to its original epitope. In addition, the art discloses that amino acids outside the CDRs are critical for antigen binding.

The specification does not disclose any other antibody besides the antibody comprising the amino acid sequences of SEQ ID NOs: 1 and 3 that can specifically bind to an epitope of an antigen expressed by at least one of HT-29, CACO-2, COLO-320 or COLO-678 cells, wherein CM-1 antibody specifically binds to said epitope of the antigen expressed by at least one of HT-29, CACO-2, COLO-320 or COLO-678 cells. Furthermore, the specification does not disclose which amino acids can be inserted or deleted in the antibody comprising the amino acid sequences of SEQ ID NOs: 1 and 3 in order for the antibody to maintain ability to specifically bind to an epitope of an antigen expressed by at least one of HT-29, CACO-2, COLO-320 or COLO-678 cells, wherein CM-1 antibody specifically binds to said epitope of the antigen expressed by at least one of HT-29, CACO-2, COLO-320 or COLO-678 cells. The genusof antibodies include antibodies in which one or more amino acids of the CDRs have been deleted or an insertion has been made in one or more of the CDRs.

It is also important to note that the epitope recognized by the claimed antibody is not disclosed. Thus, it is inferred that the actual epitope recognized by the claimed antibody is not known.

Although the disclosure of SEQ ID NO:3 and SEQ ID NO:1 combined with knowledge in the art would have put one in possession of antibodies comprising a

heavy chain variable region sequence having at least 90 sequence identity to SEQ ID NO:1, and a light chain variable region sequence having at least 90% sequence identity to SEQ ID NO:3, one of ordinary skill in the art would not be able to identify without further testing which of those amino acids can be deleted and maintain the ability to specifically binds to the epitope of the antigen expressed by at least one of HT-29, CACO-2, COLO-320 or COLO-678 cells, wherein CM-1 antibody specifically binds to said epitope of the antigen expressed by at least one of HT-29, CACO-2, COLO-320 or COLO-678 cells.

Thus, the specification does not provide an adequate written description of the genus antibodies of antibodies of claims 80-94 that is required to practice the claimed invention. Applicants have not described the genus of antibodies sufficiently to show they had possession of the claimed genus of antibodies.

Claims 100 and 101 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Claim 100 is drawn to a purified antibody comprising the amino acid sequence of SEQ ID NO:1. Claim 101 is drawn to a purified antibody comprising the amino acid sequence of SEQ ID NO:3.

The specification disclose a purified antibody comprising a heavy chain variable region sequence having the amino acid sequence of SEQ ID NO:1 and a light chain variable region sequence having an amino acid sequence of SEQ ID NO:3.

The state of the prior art is such that it is well established in the art that the formation of an intact antigen-binding site of antibodies routinely requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, cited previously). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and

affinity, which is characteristic of the immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30).

One cannot extrapolate the teaching of the specification to the enablement of the claims because the specification does not provide examples or guidance for using a purified antibody comprising the amino acid sequence of SEQ ID NO:1 or a purified antibody comprising the amino acid sequence of SEQ ID NO:3. The specification only disclose a purified antibody comprising a heavy chain variable region sequence having the amino acid sequence of SEQ ID NO:1 and a light chain variable region sequence having an amino acid sequence of SEQ ID NO:3 that specifically binds to an epitope of an antigen expressed by at least one of HT-29, CACO-2, COLO-320 or COLO-678 cells. .There are no examples of any other antibody other than an antibody comprising a heavy chain variable region sequence having the amino acid sequence of SEQ ID NO:1 and a light chain variable region sequence having an amino acid sequence of SEQ ID NO:3 The specification does not provide a nexus between a purified antibody comprising the amino acid sequence of SEQ ID NO:1, a purified antibody comprising the amino acid sequence of SEQ ID NO:3 and the and the ability to use the antibodies.

It is also important to note that the epitope recognized by the claimed antibody is not disclosed. Thus, it is inferred that the actual epitope recognized by the claimed antibody is not known.

Given the disclosure of the specification and the teaching in the art that discloses the requirements for antibody binding, one skilled in the art could not predictably use a purified antibody comprising the amino acid sequence of SEQ ID NO:1 or a purified antibody comprising the amino acid sequence of SEQ ID NO:3.

Therefore, in view of the breadth of the claims, lack of guidance in the specification, the absence of working examples, and the state of the art, it would require

undue experimentation for one skilled in the art to practice the invention as broadly claimed.

Amended claims 100 and 101 to include the functional language "that specifically binds to an epitope of an antigen expressed by at least one of HT-29, CACO-2, COLO-320 or COLO-678 cells, wherein CM-1 antibody specifically binds to said epitope of the antigen expressed by at least one of HT-29, CACO-2, COLO-320 or COLO-678 cells" would obviate this rejection.

Summary

Claims 79-101 and 103 are rejected.

Claim 102 is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Halvorson, PhD whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Mark Halvorson/
Examiner, Art Unit 1642